

Original article

Low-dose inhaled budesonide once or twice daily for 27 months in children with mild asthma

This study is an extended follow-up for 24 months of a 12-week trial to study the long-term clinical efficacy of low-dose inhaled budesonide (BUD) once or twice daily in children with mild asthma. A total of 122 children (mean age 9.7 years, girls/boys; 42/80) with mild asthma (FEV_1 103.7% of predicted, reversibility in FEV_1 3.5%, and fall in FEV_1 after exercise 12.2%), not previously treated with inhaled steroids, were included in a double-blind, randomized, parallel-group study. The children were treated with inhaled BUD 100 or 200 µg administered via Turbuhaler® once daily in the morning, 100 µg twice daily, or placebo for 27 months. Exercise and methacholine challenges were performed at 3-month intervals the first year and at 6-month intervals the second year, in a total of seven visits. A significant dose-response effect favoring BUD 200 µg daily (vs 100 µg daily) was found when comparing changes in FEV_1 , $FEF_{25\%}$, and $FEV_{50\%}$; the fall in FEV_1 after an exercise test; and the effect on blood eosinophils. Bronchial hyperreactivity to methacholine decreased significantly on three visits in patients treated with BUD 200 µg daily compared to placebo. Growth rate was not significantly affected except in children aged 7–11 years at baseline after 12 months of treatment. In conclusion, 100 or 200 µg daily of inhaled BUD for 27 months is safe and effective in protecting against exercise-induced asthma and achieving nearly normal lung function. Baseline lung function was not significantly affected in this group of children with mild asthma.

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Inflammatory changes in the mucosal membranes of the lower airways in asthmatic patients are now considered to be the major pathophysiologic basis of the morbidity of the disease (1), and have been shown to occur also in mild, intermittent asthma (2, 3). Long-term studies in children with asthma have shown that early anti-inflammatory treatment may prevent a decline in lung function (4, 5). International treatment recommendations currently suggest treating mild, persistent childhood asthma with a low dose of either inhaled steroids, cromolyn sodium, or nedocromil sodium (6, 7). Glucocorticosteroids are the most effective anti-inflammatory

drugs in the treatment of asthma. The recommended dose of inhaled steroid for the treatment of mild asthma has been 50–200 µg twice daily (8).

In recent years, however, four randomized, placebo-controlled studies in children, in which asthma was treated with moderate doses of beclomethasone dipropionate (BDP) (i.e., 400 µg/day), have reported decreased growth velocity after 7–12 months of treatment (9–12). At a daily dose of 200 µg of BDP or BUD, no reports of long-term side-effects have been published (13). If childhood asthma is treated with inhaled steroids, the goal should therefore be to use the lowest possible dose compatible with optimal disease control, and it has been maintained that it is preferable to use only one prophylactic compound in order to achieve good therapeutic compliance (7).

In the present paper, we describe the extension of a randomized, double-blind, placebo-controlled trial reported previously (14), involving a 2-year follow-up of children with mild asthma treated with 100 or 200 µg inhaled BUD per day.

Abbreviations. BUD 100 o.d.: budesonide 100 µg once daily; BUD 200 o.d.: budesonide 200 µg once daily; BUD 100 b.i.d.: budesonide 100 µg twice daily; PEF: peak expiratory flow; FEV_1 : forced expiratory volume in 1 s; $FEF_{25\%}$: forced expiratory flow at 25% of forced vital capacity; R_{tot} : total airway resistance; G_{tot} : total airway conductance, calculated as $1/R_{tot}$; ECP: eosinophil cationic protein.

Material and methods

Study design

The study was a double-blind, placebo-controlled, single-center extension trial. The study was the direct continuation of a previous 12-week trial ($n=163$), which has been reported and described in detail elsewhere (14). All patients in the present study were already randomized into four parallel groups in balanced blocks 3 months before inclusion in the present study. At randomization, each patient had received two Turbuhaler inhalers, one to be used in the morning and the other in the evening. Group I patients were given BUD 100 µg once daily in the morning and placebo in the evening. Group II received BUD 200 µg once daily in the morning and placebo in the evening. Group III received BUD 100 µg twice daily. The remaining group, group IV, received placebo twice daily. Clinical assessments, including lung-function tests (flow-volume curve and plethysmography), blood sampling, exercise tests, and measurement of PD₂₀ methacholine were performed at 3-month intervals in the first year and at 6-month intervals in the second year. The exercise test and the methacholine provocation were performed on separate days. Skin prick tests were performed at visit 1 or 2. During the last 2 weeks before clinical visits, the patients were asked to keep daily records of peak flow values, symptoms, use of β₂-agonists, and intake of study medication. Baseline values for patients participating in the study were obtained at randomization (i.e., before the start of the previous 12-week trial); hence, there was a total study period of 27 months.

The study was approved by the Regional Medical Ethics Committee in Oslo (Norway), and written informed consent was obtained from the parents or guardians of all patients.

Patients

A total of 122 children with mild asthma were included in the study, 80 boys and 42 girls, aged 7–16 years. All children had been randomized 12 weeks earlier to one of four different treatment groups in a preceding trial, and had been selected from the outpatient clinic at the Section of Allergy and Pulmonology, Department of Paediatrics, Ullevål University Hospital, Oslo. The inclusion criterion for the present study was to have participated in and completed the initial 12-week trial. All children fulfilling this criterion were invited to participate in the present study and to continue with the same treatment for the following 24 months. The inclusion criteria for the 12-week trial included a diagnosis of asthma based on the definition in the International Consensus report (15) and in the Nordic Consensus report (16), with three previous obstructive episodes or one previous obstructive episode with

atopy. At least one of these episodes had to have occurred within the last year before randomization. The patients had not used inhaled steroids within 2 months, or cromoglycate and/or nedocromil within 4 weeks of entry.

Methods

Participants in the study were instructed to inhale BUD (daily dose 100 or 200 µg) or placebo from Turbuhaler® inhalers (Astra Draco, Lund, Sweden), in the morning and evening during the whole treatment period. They were instructed to rinse their mouths with water after each use. All patients were supplied with terbutaline (Bricanyl Turbuhaler®, 250 µg), to be used as needed during the study. The use of long-acting β₂ agonists was not allowed in the study. A peak expiratory flow (PEF) meter (Vitalograph, Ennis, Ireland) had been dispensed in the earlier trial and was used in the present study. Children were required to demonstrate that they were competent in using Turbuhaler and the PEF meter correctly at every clinical visit during the study. Patients were instructed to fill in a diary twice daily during the first 3 months of the study, and thereafter the last 2 weeks before each visit, recording intake of study medication as well as rescue medication, PEF values, and symptom score. The highest PEF value from three exhalations was recorded on each occasion. Asthma symptoms were scored on a four-point scale, which ranged from 0 (no symptoms) to 3 (severe symptoms). The diary sheet was collected at every visit.

Exercise-induced bronchoconstriction (EIB) was determined at all visits by a run for 6 min with submaximal exercise load, on a motor-driven treadmill (17). The inclination of the treadmill was 5.5%, and the speed was adjusted to submaximal load to achieve a steady-state heart rate of at least 170 beats per min at every visit. The cardiac frequency was recorded electronically (Sport-Tester® PE 3000 with memory function: Polar Electro KY, Kempele, Finland). The treadmill run was performed at a speed needed to achieve a heart rate (exercise load) comparable to the previous treadmill test for the individual child. FEV₁ was measured before running, and immediately after and 3, 6, 10, and 15 min after running. Maximum percentage fall in FEV₁ after the exercise test was calculated by the following formula:

$$\frac{(\text{pre-exercise FEV}_1 - \text{minimum post-exercise FEV}_1)}{\text{pre-exercise FEV}_1}$$

× 100

Bronchial hyperreactivity was measured at all visits by the methacholine chloride inhalation test for determination of PD₂₀ (18). Methacholine was inhaled in doubling doses from 0.128 µmol up to a maximum

dose of 16.32 μmol , or until FEV_1 had fallen 20% or more compared with FEV_1 after an initial saline (0.9%) inhalation. The bronchial aerosol provocation system (APS) (Jaeger, Würzburg, Germany) with the Sandoz nebulizer (Jaeger) was used for this procedure. The Sandoz nebulizer was calibrated to nebulize 5 μl per nebulization and was triggered by inspiration at tidal ventilation. Each nebulization lasted for 0.5 s. Lung function was measured 1 min after each inhaled dose. PD_{20} was determined by linear interpolation on a semilogarithmic scale (19).

If the patient had inhaled a β_2 -agonist during the last 8 h before the lung-function tests were to be performed, the challenge was postponed to the next day.

Lung function was measured at every visit by maximal forced expiratory flow-volume curves and whole-body plethysmography (Masterlab Body, Jaeger) under body temperature, barometric pressure, saturated with water vapor (BTPS) conditions. Predicted lung-function values were calculated with reference values from Zapletal et al. (20). At least three independent flow-volume curves were obtained at each visit, and the curve with the highest FEV_1 was chosen. Values for $\text{FEF}_{25\%}$, $\text{FEF}_{50\%}$, and $\text{FEF}_{75\%}$ were also registered from the selected flow-volume curves. Calibrations were carried out daily on all lung-function measuring equipment used in the study.

Growth velocity was determined from measurements of patient height at every visit throughout the study period by a wall-fixed stadiometer (Seca, Hamburg, Germany). Three trained persons carried out all height measurements during the study. The child was measured standing upright without shoes with the heels touching the wall to which the stadiometer was fixed. The moveable part of the measuring device was placed lightly on the child's head before the child's height was read from a centimeter scale. At baseline, the patient's height was measured by two persons, and the mean value was registered. One patient (in the BUD 100 μg once daily group) who had reached final height (2.02 m) at baseline was not included in growth analysis.

Patient compliance was assessed by counting the remaining doses in the inhaler device, which initially contained 200 doses. This was done at every 6-month interval or when the inhalers were returned. This method has been described in detail elsewhere (21). Compliance was calculated by the following formula:

% compliance =

$$\frac{200 - \text{number of remaining doses} \times 100}{\text{number of prescribed doses}}$$

Laboratory tests including complete blood count and eosinophil count were done at every visit. Eosinophil cationic protein (ECP) (Pharmacia Diagnostics,

Uppsala, Sweden) was measured during the first 3 months of the study. Blood samples were kept for 1 h at room temperature and then centrifuged to separate serum and blood corpuscles. The blood samples were labeled and frozen at -70°C .

Skin prick tests were performed according to the Nordic guidelines (22) with the following allergens: house-dust mite (*Dermatophagoides pteronyssinus*), mold (*Cladosporium herbarum*), birch pollen, grass pollen (timothy), cat dander, and dog dander (Soluprick, ALK, Copenhagen, Denmark). To be considered allergic to an allergen, a subject had to have a positive skin prick test of at least ++ (50% of the reaction to histamine 10 mg ml^{-1}).

Asthma exacerbation was defined as mild when increased symptoms could be reversed by the additional use of a β_2 -agonist alone. Severe exacerbation was defined as an acute episode of increasing symptoms requiring additional therapy other than β_2 -agonists. Patients were then treated with either inhaled BUD 400 μg twice daily for 2 weeks in addition to β_2 -agonists or sometimes in addition to a systemic glucocorticosteroid (prednisolone 1 mg/kg body weight, maximal dose 40 mg, daily) for 1–3 days. A patient was withdrawn from the study if he or she had three or more mild exacerbations in 3 months or two or more severe ones in 6 months.

Adverse event information was obtained at each visit by asking the patients or their guardians, "Have you/your child had any health problems or symptoms not usually associated with your/his/her asthma since the last visit?" The onset, severity, and outcome of each adverse event were recorded. All hospital admissions during the study period were considered serious adverse events.

Sample size

The sample size for the study was calculated with the aim of detecting a difference between the active groups and the placebo group in FEV_1 , percent of predicted. If the difference between means was set to be at least 8%, the standard deviation to 11%, the type I error to 5%, and the type II error to 20%, the minimum number of patients needed in each group was calculated to be 30. The calculation was based on two-tailed *t*-tests conducted at the 5% significance level, on the assumption of equal variance in the groups and normally distributed data.

Statistical evaluation

The treatment effect at the end of treatment was analyzed by analysis of covariance (ANACOVA) with treatment as a factor and baseline value as a covariate. In some instances, the change from baseline to the end of treatment was of interest. In this case, the individual difference between the baseline values and the end of

treatment values was calculated. This difference was used in analysis of variance (ANOVA) with treatment as the only factor. The ANACOVA or the ANOVA models were used to obtain estimates for pairwise differences with standard deviation and *P* values in order to calculate a 95% confidence interval.

An additive model was used when analyzing diary variables, lung-function variables, and the maximum fall in FEV₁ after the exercise test, whereas a multiplicative model was used when analyzing plethysmography variables and PD₂₀. The effects of BUD 100 µg once daily and placebo were compared by a two-sided *t*-test. The effects of BUD 200 µg once daily and BUD 100 µg once daily were compared in the same manner. Differences in categoric variables were assessed by chi-square test. The statistical analysis was carried out on the intention-to-treat principle; thus, all patients receiving at least one dose of study medication were included. Missing values for withdrawals were handled by the last value extended principle. All tests were two-sided, and *P* values below or equal to 0.05 were considered to be significant.

Results

Between May 1995 and June 1996, 122 patients (80 boys, 42 girls) were enrolled in the study. Patient characteristics at baseline were comparable in the four treatment groups, as shown in Table 1, without statistically significant difference between the groups. Thirty-three patients withdrew during the 2-year study period. Nineteen patients withdrew due to disease deterioration, two from the BUD 100 µg twice daily group, three from the BUD 100 µg once daily group, six from the BUD 200 µg once daily group, and eight from the placebo group. Withdrawals due to noncompliance were, respectively, four, three, and two from the BUD groups and five from the placebo group. This difference between

treated and placebo was not significant. One patient from the BUD 100 µg twice daily group withdrew due to change of residence in the study period.

Exercise-induced bronchoconstriction (EIB)

The mean maximum fall in FEV₁ (% fall from pre-exercise value) after the exercise test at baseline is presented in Table 1. Pairwise comparison between the BUD groups and placebo at different treatment intervals revealed statistically significant differences at all visits except at 9 months for the BUD 100 µg twice daily group, and all except 9 and 27 months for the BUD 200 µg once daily group, whereas the BUD 100 µg once daily group revealed significant differences only at 3, 6, and 12 months, as shown in Table 2. Comparison between the three BUD groups at all visits revealed only one statistically significant difference at 21 months in favor of the BUD 100 µg twice daily group over the BUD 200 µg once daily group. The change from baseline in the mean maximum fall in FEV₁ (%) was consistently higher for all individual treatment groups (−10.7 [SD; 14.2] to −4.5 [SD; 10.3]) at all visits compared to placebo (−2.9 [SD; 12.0] to 1.7 [SD; 10.8]), and the change from baseline in maximum fall in FEV₁ (%) between all BUD groups taken together was significant at all visits when compared to placebo (Fig. 1).

Methacholine hyperreactivity

The mean percentage increase in PD₂₀ to methacholine (µmol) from baseline to the end of treatment was 227% for the BUD 100 µg twice daily group, 119% for the BUD 200 µg once daily group, 128% for the BUD 100 µg once daily group, and 73% for the placebo group. Pairwise comparison of active treatment and placebo revealed statistically significant differences at 12 and 21 months for the BUD 100 µg twice daily group, and at 21 months for the BUD 200 µg once daily

Table 1. Patient characteristics at baseline per treatment group

Characteristics	BUD 100 b.i.d.	BUD 200 o.d.	BUD 100 o.d.	Placebo
Number of patients	28	32	28	34
Boys/girls	18/10	17/15	23/5	22/12
Age (years)	10.2	10.0	9.5	9.4
Height (cm)	145.6	145.6	139.3	138.7
Number of atopsics	20	21	20	26
FEV ₁ (l)	2.27 (0.57)	2.23 (0.66)	2.30 (0.85)	2.04 (0.67)
FEV ₁ % of pred.	106.0 (14.1)	102.1 (11.4)	102.2 (12.8)	104.6 (12.9)
Reversibility in FEV ₁ (%)	4.3 (3.8)	3.6 (3.4)	2.4 (2.8)	3.8 (3.1)
PEF morning (l/min)	263.8 (62.2)	260.4 (84.2)	259.9 (85.4)	229.5 (75.9)
PEF morning % of pred.	86.1 (19.0)	89.6 (15.6)	85.7 (14.8)	87.4 (12.4)
ECP	16.9 (13.1)	19.3 (12.3)	19.8 (15.9)	14.2 (12.1)
Methacholine PD ₂₀ (µmol)	3.75	4.33	5.83	4.04
Maximum fall in PEV ₁ (%) after exercise test	10.6 (8.1)	13.7 (12.4)	14.7 (17.5)	10.1 (9.6)

Results are given as mean values with SD in parenthesis.

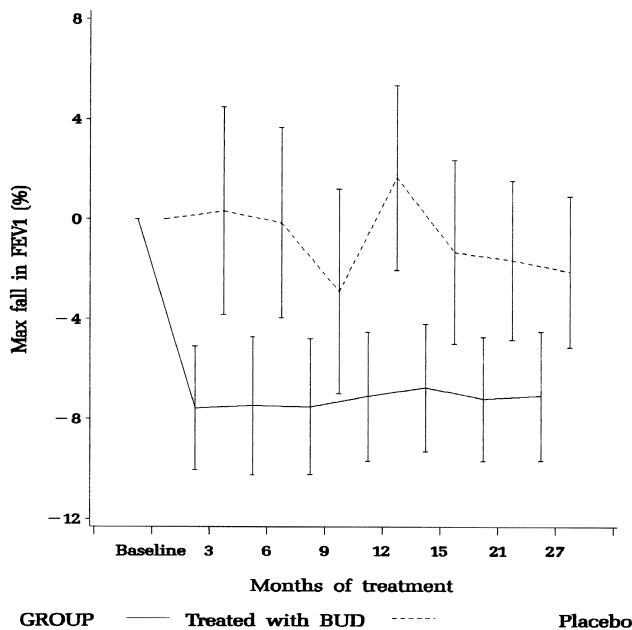


Figure 1. Comparison between different treatment effects on change from baseline in maximum fall in FEV₁ after exercise test (mean [95% CI]).

group, as presented in Table 3. No significant difference between the BUD groups was found at any visit. Geometric mean values for PC₂₀ to methacholine (μmol) expressed as the change from the baseline value for joined treatment groups *vs* placebo in doubling doses are shown in Fig. 2, and they were not significant ($P=0.13$ at 12 months and 0.08 at 21 months).

Lung function

A statistically significant difference ($P=0.01$ – 0.02) was found between BUD 100 μg twice daily and placebo for FEV₁ at all visits throughout the study period. A similarly significant effect on FEF_{25%} and FEF_{50%} for this treatment group was found on all visits, as well as after 3, 21, and 27 months of treatment for FEF_{75%}. No significant difference regarding effect on FEV₁ was found when BUD 100 μg twice daily was compared to BUD 200 μg once daily. Comparison between the estimated effect of 200 and 100 μg daily of BUD on

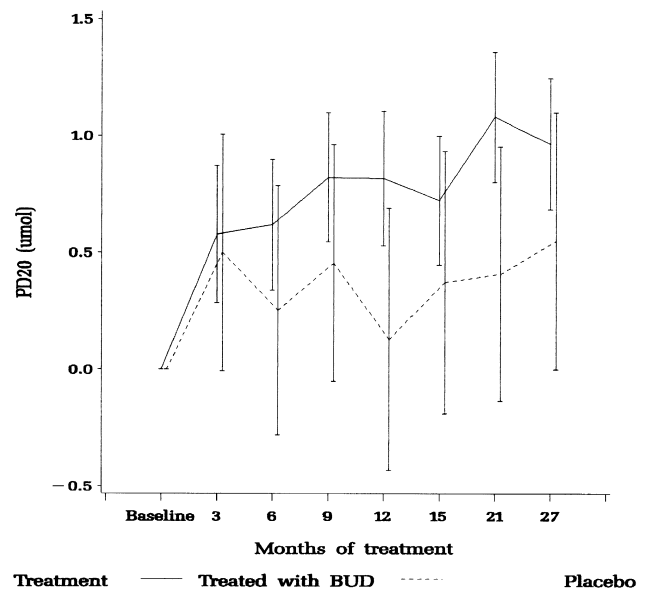


Figure 2. Changes in airway responsiveness (PD₂₀) in doubling doses (mean, 95% CI) from baseline during treatment with budesonide 100 or 200 μg daily or placebo for 27 months.

FEV₁ revealed a significantly ($P=0.008$ – 0.048) better effect of the higher BUD dose on all visits from 9 months to the end of the study period.

FEV₁ percent predicted declined (change from baseline) in all treatment groups; -2.5% (BUD 100 b.i.d.), -5.2% (BUD 200 o.d.), and -8.2% (BUD 100 o.d.), with -8.6% for the placebo group. This difference between BUD treatment and placebo was significant only at 12 and 27 months, in favor of the BUD 100 μg twice daily group on both occasions. Comparing the treatment effect of 100 or 200 μg BUD daily with placebo on the change from baseline of FEV₁ percent predicted revealed a significantly better effect of 100 μg daily during the first 12 months of the study ($P=0.007$ at 3 months and 0.02 at 12 months), whereas an increasing difference in favor of 200 μg daily was found from that point on, reaching significance at the end of the study ($P=0.03$).

When treatment groups were compared to placebo, no consistently significant difference was found in measured effect on airway conductance (Gaw) or resistance in the respiratory system (Rrs) in pairwise comparison between the treatment groups or placebo.

Table 2. Estimated difference in fall in FEV₁ (%) after exercise test at different treatment intervals (% fall from pre-exercise value)

Months	BUD 100 b.i.d. – placebo	BUD 200 o.d. – placebo	BUD 100 o.d. – placebo
3	-5.15 (-9.40 – -0.9)*	-4.98 (-9.20 – -0.8)*	-4.84 (-8.90 – -0.80)*
6	-5.42 (-9.30 – -1.6)**	-4.45 (-8.30 – -0.6)*	-5.01 (-8.70 – -1.30)**
9	-3.24 (-7.50 – 1.0)†	-1.27 (-5.50 – 3.0)†	-2.65 (-6.80 – 1.40)†
12	-8.01 (-12.8 – -3.2)**	-5.97 (-10.7 – -1.3)*	-7.18 (-11.8 – -2.60)**
15	-4.60 (-8.90 – -0.3)*	-4.54 (-8.80 – -0.3)*	-1.72 (-5.90 – 2.50)†
21	-6.05 (-9.90 – -2.2)**	-4.20 (-8.00 – -0.4)*	-1.13 (-4.80 – 2.58)†
27	-4.65 (-8.10 – -1.2)**	-2.78 (-6.22 – 0.7)†	-1.39 (-4.70 – 1.95)†

95% confidence intervals are given in parenthesis. * $P<0.05$; ** $P<0.01$; † Nonsignificant.

Long-term treatment with inhaled steroids in childhood asthma

Table 3. Comparison between different treatment effects on provocative dose of methacholine (μmol) causing 20% fall in forced expiratory volume in 1 s: estimated ratio (%) between treatment effects after 3–27 months of therapy

Months	BUD 100 b.i.d. vs placebo	<i>P</i> value	BUD 200 o.d. vs placebo	<i>P</i> value	BUD 100 o.d. vs placebo	<i>P</i> value
3	155% (76–315)	0.23	89% (45–176)	0.73	94% (46–191)	0.86
6	178% (88–360)	0.12	136% (69–268)	0.37	124% (61–252)	0.54
9	190% (96–377)	0.07	136% (70–264)	0.35	116% (58–230)	0.67
12	237% (114–494)	0.02	191% (94–386)	0.07	174% (84–362)	0.14
15	192% (95–391)	0.07	123% (62–244)	0.55	122% (60–248)	0.58
21	225% (111–457)	0.02	203% (103–402)	0.04	162% (80–329)	0.18
27	189% (93–386)	0.08	135% (68–269)	0.39	138% (68–281)	0.38

CI: 95% confidence interval; BUD: budesonide.

Laboratory tests

Mean ECP values at baseline are given in Table 1. After 3 months of treatment, ECP decreased by 13.0% in the BUD 100 μg twice daily, 13.5% in the BUD 200 μg once daily, and 10.6% in the BUD 100 μg once daily group, whereas an increase of 12.6% was found in the placebo group. This difference in the change from baseline was on the border of significance when BUD 200 μg daily was compared to placebo ($P=0.05$), but was not significant between BUD 100 μg daily and placebo ($P=0.23$).

After 3 months, patients treated with BUD had a significantly ($P=0.02$ – 0.05) lower blood eosinophil count at all except one visit (27 months; $P=0.22$). Comparison between the three individual BUD groups revealed no significant differences, but, as shown in Table 4, treatment with 200 μg daily was significantly more effective than 100 μg daily when compared to placebo at all visits between 9 and 21 months.

Symptom scores/asthma exacerbations

Mean values for asthma symptom scores were low at baseline in all treatment groups. From baseline to the end of the study, asthma symptoms during daytime declined from 0.4 to 0.06 (85% decrease) in the group receiving 200 μg daily, from 0.47 to 0.18 (62% decrease) in the group receiving 100 μg daily, and from 0.37 to 0.13 (65% decrease) in the placebo group. Asthma symptoms during the night were likewise reduced in

respective groups by 80%, 87%, and 44%. The mean use of rescue medication at baseline was 0.6 inhalations per 24 h^{-1} .

The number of mild/severe asthma exacerbations was 40/6 in the BUD 200 μg once daily group, 40/2 in the BUD 100 μg twice daily group, 40/4 in the BUD 100 μg once daily group, and 50/13 in the placebo group (NS).

Compliance

Compliance data from the present study have been reported elsewhere (23). The mean measured compliance for morning medication dropped significantly ($P<0.05$) from 77% after 3 months of treatment to 52% 6 months later. Evening medication compliance dropped respectively from 78% to 59% in the same period. Compliance declined further to 42% for morning medication and 46% for evening medication during the last 6 months of the study. Drug compliance declined more rapidly in the placebo group than for active treatment, and this difference became significant after 2 years of treatment.

Adverse events

Serious adverse events were registered 10 times, and all were hospital admissions due to causes not related to asthma. All patients recovered fully and a causal relationship to the study drug was judged unlikely by the investigator. No patient was excluded from the study due to a serious adverse effect.

Table 4. Comparison between different treatment effects on estimated difference in number of blood eosinophils at different intervals for 27 months

Months	BUD 200 μg daily* vs placebo	<i>P</i> value	BUD 100 μg daily vs placebo	<i>P</i> value
3	−0.03 (−0.1 – 0.1)	NS	0.02 (−0.1 – 0.6)	NS
6	−0.08 (−0.2 – 0.0)	NS	−0.07 (−0.2 – 0.1)	NS
9	−0.17 (−0.3 – −0.1)	<0.001	−0.08 (−0.2 – 0.0)	NS
12	−0.12 (−0.2 – −0.0)	0.03	−0.05 (−0.2 – 0.1)	NS
15	−0.12 (−0.2 – −0.0)	0.02	−0.05 (−0.2 – 0.1)	NS
21	−0.11 (−0.2 – −0.0)	0.02	−0.08 (−0.2 – 0.0)	NS
27	−0.07 (−0.2 – 0.0)	NS	−0.02 (−0.1 – 0.1)	NS

Adjusted means from analysis of variance and 95% confidence interval (CI). BUD: budesonide; NS: nonsignificant.

*This group consisted of two groups: BUD 100 b.i.d. and BUD 200 μg once daily.

Mean annual linear growths during the first and second years of the study period were, respectively, 5.97 cm (SD: 2.02) and 5.38 cm (SD: 1.82) in the BUD-treated subjects *vs* 6.48 cm (SD: 0.98) and 6.17 cm (SD: 1.13) in the placebo group. The estimated difference between treated and placebo was 0.64 (95% CI: -0.33 to 1.62) (NS) for the first year, and 0.72 (95% CI: -0.26 to 1.70) (NS) for the second year. The estimated difference in growth rate for children aged 7–11 years at baseline treated with BUD ($n=39$ after 1 year and $n=19$ after 2 years) or placebo ($n=17$ after 1 year and $n=9$ after 2 years) revealed significant differences at all visits after 12 months of treatment (estimated difference 1.09–1.49, 95% CI: 0.33–2.22) ($P=0.006$ – 0.001). In this group of patients, the growth velocity was significantly lower in boys than girls ($P<0.03$) after treatment for 9 and 12 months.

Discussion

The present study has provided information on long-term treatment of mild childhood asthma with a low dose of inhaled steroids. It shows that 100 or 200 μg daily treatment with BUD can significantly protect against EIB, and that this effect is maintained for 27 months of treatment. A significant dose-response effect was found in favor of the 200 μg daily dose on lung-function parameters (FEV_1 , $\text{FEF}_{50\%}$, and $\text{FEF}_{25\%}$), serum eosinophils, and EIB.

Children participating in the present study had mild disease; i.e., they were suffering from low-grade symptoms that did not interfere with sleep and lifestyle, or episodes of cough and wheeze occurring less than once a month (24). Disease exacerbations were treated by increasing the dose of BUD for 2 weeks at the time, and only four patients needed systemic treatment with corticosteroids (prednisolone). No included child was admitted to hospital for asthma exacerbation during the study period. Baseline lung-function values were normal (mean FEV_1 103.7% pred.) with low reversibility, giving little room for improvement in these parameters. The mean use of rescue medication at baseline was 0.6 inhalations per 24 h^{-1} . This relatively high use suggests that the children were using a bronchodilator routinely before exercise before inclusion.

Inclusion criteria did not include minimum reversibility after inhalation of a β_2 -agonist or predefined grade of bronchial hyperresponsiveness. The inclusion criteria employed in the present study may be considered to be comparable to routine clinical settings, and findings may consequently have clinical relevance for a large group of patients, since the majority of children suffering from asthma have mild disease.

The present study confirms the clinical efficacy of inhaled BUD, a conclusion which has been reported in other long-term studies in childhood (4, 25) and adult

asthma (26). However, an important difference between these studies and the present study is that higher doses (400–800 μg daily) of BUD were used in all the other studies, possibly reflecting differences in disease severity. Guidelines now recommend the use of 100–400 μg daily in the treatment of mild asthma (8). The present study suggests that a daily dose of 200 μg is safe and sufficient to reduce bronchial hyperresponsiveness and control exercise-induced symptoms, and is more effective than placebo to prevent a decline in lung function (FEV_1 percent predicted) in children with milder forms of asthma. This conclusion is, in part at least, supported by other studies which have shown that inhaled steroids in doses of 100–200 μg daily are effective in controlling symptoms in children, without causing apparent systemic side-effects (27–29). Likewise, it has been demonstrated that once daily low-dose inhaled BUD (200 μg) is as effective as 100 μg twice daily in successful management of mild asthma in adults (30).

The clear dose-response effect found in the present study indicates that 200 μg BUD daily is more effective than 100 μg daily with respect to lung function (FEV_1 , $\text{FEF}_{25\%}$, $\text{FEF}_{50\%}$, and $\text{FEF}_{75\%}$), EIB, and effect on blood eosinophils. Other studies have described similar dose-response effects on lung function and asthma symptoms in moderate to severe childhood asthma treated with different daily doses of BUD; i.e., 100, 200, or 400 μg (28), and 200, 400, or 800 μg daily (31). Both those studies found no signs of systemic side-effects of BUD in the dosages used, and this finding is supported by the present study. However, the effect on blood eosinophils in the present study is a clear indication that a daily dose of 200 μg inhaled BUD has a systemic effect in this group of patients with mild asthma. A similar effect on blood eosinophils has been reported in another double-blind placebo-controlled study, in which children with clinically stable asthma were treated with beclomethasone 400 μg daily for 12 months (12). However, that study differed from the present study in that the drug significantly affected linear growth, which was not as clearly affected in the present study.

The effect on EIB was maintained for the whole study period for the treatment groups, being most pronounced in the groups treated with 200 μg daily. At 9 months, the mean fall in FEV_1 (%) after a treadmill test was 7.2% in the placebo group, which was the lowest maximum reduction in FEV_1 of all visits (8.1–11.8%) for this group. The reason for this is unknown, but one external factor likely to contribute to this variability between clinical visits was changes in the health status of the study subjects. Patients in the placebo group were prescribed a high dose of inhaled BUD for a period of 2 weeks on 16 occasions due to asthma exacerbation, and it is possible that this treatment may in some cases have caused a transient effect on reaction to the exercise test. The results from the present study imply that the effect

on EIB relates well to the effect on blood eosinophils, whereas no such relationship to the effect on PD₂₀ of methacholine could be found.

The effect on directly measured bronchial responsiveness by methacholine inhalation (PD₂₀), which in the present study increased significantly throughout the study period in the BUD-treated children as compared to placebo, has also been reported in other studies concerning long-term treatment of childhood asthma with inhaled steroids (12, 32). However, the effect found in the present study was not of the same magnitude as in the other studies, possibly reflecting the low dose of BUD applied in the present study. This impression is supported by the fact that BUD 200 µg daily was more effective than BUD 100 µg daily compared to placebo in reducing bronchial responsiveness to methacholine.

No dose-response effect within the treatment groups was found regarding growth velocity in the present study, and significant difference was found only when comparing BUD treatment and placebo in children that were aged 7–11 years at baseline, but not for the whole treatment group. The fact that the puberty status of the participating children was not systematically evaluated during the study, as well as the fact that no data on pre-baseline growth rate were available, is likely to have a

considerable confounding effect on these findings and make it difficult to draw conclusions regarding a possible effect on growth velocity.

The fact that drug adherence in the present study declined to close to 50% after the first 9 months and to nearly 40% the last 6 months is still interesting in view of the clear efficacy of the doses used, and indicates the potency of the drug (or the steep form of the dose-response curve) with respect to the outcome measurements in this group of children with mild asthma.

In conclusion, a low dose (100 or 200 µg daily) of inhaled BUD for 27 months provided a long-lasting, dose-response effect in protecting against EIB, reducing the number of blood eosinophils, and, to a lesser extent, reducing bronchial hyperresponsiveness to methacholine in a group of children with mild asthma and nearly normal lung function.

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References

1. BOUSQUET J, CHANEZ P, VIGNOLA AM, LACOSTE JY, MICHEL FB. Eosinophil inflammation in asthma. *Am J Respir Crit Care Med* 1994;**150**:S33–S38.
2. VIGNOLA AM, CHANEZ P, CAMPBELL AM, et al. Airway inflammation in mild intermittent and in persistent asthma. *Am J Respir Crit Care Med* 1998;**157**:403–409.
3. BEASLEY R, ROCHE WR, ROBERTS JA, HOLGATE ST. Cellular events in the bronchi in mild asthma and after bronchial provocation. *Am Rev Respir Dis* 1998;**139**:806–817.
4. AGERTOFT L, PEDERSEN S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;**88**:373–381.
5. KÖNIG P, SHAFFER J. The effect of drug therapy on long term outcome of childhood asthma: a possible preview of the international guidelines. *J Allergy Clin Immunol* 1996;**98**:1103–1111.
6. Expert Panel Report II. Guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program. National Institutes of Health, February 1997.
7. WARNER JO, NASPITZ CK. Third International Paediatric Consensus Statement on the Management of Childhood Asthma. *Pediatr Pulmonol* 1998;**25**:1–17.
8. WOODHEAD M. Guidelines on the management of asthma. *Thorax* 1993;**48**:S1–S26.
9. DOULL IJM, FREEZER NJ, HOLGATE ST, DOULL IJ. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;**151**:1715–1719.
10. TINKELMAN DG, REED CE, NELSON HS, OFFORD KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;**92**:64–77.
11. VERBERNE AA, FROST C, ROORDA RJ, VAN DER LAAG H, KERREBIJN KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1997;**156**:688–695.
12. SIMONS FE. Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med* 1997;**337**:1659–1665.
13. KAMADA AK, SZEFLER SJ. Glucocorticoids and growth in asthmatic children. *Pediatr Allergy Immunol* 1995;**6**:145–154.
14. JÖNSSON G, CARLSEN KC, BLOMQUIST P. Clinical efficacy of low-dose inhaled budesonide once or twice daily in children not previously treated with steroids. *Eur Respir J* 1998;**12**:1099–1104.
15. SHEFFER AL, BOUSQUET J, BUSSE WW, et al. International consensus report on diagnosis and treatment of asthma. *Eur Respir J* 1992;**5**:601–641.
16. Nordic consensus report. In: Nordiska samarbetsnämnden för Medicinsk Forskning (NOS). Stockholm: Sprit 1992:19–20.
17. OSEID S, HAALAND K. Exercise studies on asthmatic children before and after regular training. In: ERIKSSON B, FURBERG B, editors. *Swimming medicine IV*. Baltimore, MD: University Park Press, 1978:32–41.

18. YAN K, SALOME C, WOOLCOCK AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983;**38**: 760–765.
19. COCKCROFT DW, BERSCHIED BA. Slope of the dose-response curve: usefulness in assessing bronchial responses to inhaled histamine. *Thorax* 1983;**38**:55–61.
20. ZAPLETAL A, SAMANEK M, TUMA S, RUTH C, PAUL T. Assessment of airway function in children. *Bull Physiopathol Respir* 1972;**8**:535–543.
21. JÓNASSON G, CARLSEN KH, SØDAL A, JONASSON C, MOWINCKEL P. Patient compliance in a clinical trial with twice daily inhaled budesonide or placebo in children with mild asthma. *Eur Respir J* 1999;**14**:150–154.
22. AAS K, BELIN L. Standardization of diagnostic work in allergy. First report from the standardization committee of the Northern Society of Allergology, 1971. *Acta Allergol* 1972;**27**:439–468.
23. JÓNASSON G, CARLSEN K-H, MOWINCKEL P. Asthma drug adherence in a long-term clinical trial. *Arch Dis Child* 2000 (in press).
24. WARNER JO, NEIJENS H, LANDAU LI. Asthma: a follow up statement from an international paediatric asthma consensus group. *Arch Dis Child* 1992;**67**:240–248.
25. VAN ESSEN-ZANDVLIET EE, HUGHES MD, WAALKENS HJ, DUIVERMAN EJ, KERREBIJN KF. Remission of childhood asthma after long-term treatment with an inhaled corticosteroid (budesonide): can it be achieved? *Eur Respir J* 1994;**7**:63–68.
26. WEINER P, WEINER M, AZGAD Y. Long-term clinical comparison of single versus twice daily administration of inhaled budesonide in moderate asthma. *Thorax* 1995;**50**:1270–1273.
27. PRICE JF, WELLER PH. Comparison of fluticasone propionate and sodium cromoglycate for the treatment of childhood asthma (an open parallel group study). *Respir Med* 1995;**89**: 363–368.
28. PEDERSEN S, HANSEN OR. Budesonide treatment of moderate and severe asthma in children: a dose response study. *J Allergy Clin Immunol* 1995;**95**:29–33.
29. VOLOVITZ B, AMIR J, MALIK H. Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. *N Engl J Med* 1993;**329**:1703–1708.
30. CHISHOLM SL, DEKKER FW, KNUISTINGH NA, PETRI H. Once-daily budesonide in mild asthma. *Respir Med* 1998;**92**: 421–425.
31. SHAPIRO G, BRONSKY EA, LAFORCE CF, et al. Dose-related efficacy of budesonide administered via a dry powder inhaler in the treatment of children with moderate to severe persistent asthma. *J Pediatr* 1998; **132**:976–982.
32. VAN ESSEN-ZANDVLIET EE, HUGHES MD, WAALKENS HJ, DUIVERMAN EJ, POCKOCK SJ, KERREBIJN KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis* 1992;**146**:547–554.